Title: Volume-Based Referral for Cardiovascular Procedures in the United States: A Cross-sectional Regression Analysis

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Author's response to reviews: see over
Authors’ response to reviews

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Note that, thanks to reviewer comments, a bug in the algorithm to measure the use of IMA grafts during CABG surgery was corrected. The proportion of CABG surgeries involving the use of IMA grafts rose to about 77%. As a result, the risk-adjusted CABG mortality model was re-estimated and the number of deaths averted from moving all CABG surgeries to high-volume hospitals was re-calculated. The results changed minimally. See below for more discussion of this issue.
Response to Comments from Reviewer 1, Peter Bogaty

General:
This is an interesting paper that provides a contemporary analysis and perspective on the consequences and implications of performing CABG and PCI in high volume versus low volume centers given the higher mortality associated with the latter. The conclusion after appropriate analysis is that this is unlikely to be cost-effective given the large numbers needed to save lives (since absolute mortality differences are small) and the fragility of the assumptions on which this is based.

No response required.

Major Compulsory Revisions:
None

Minor Essential Revisions:
None

Discretionary Revisions:
It would be useful if the authors could provide 95% CI on the numbers of patients that would require transfer to save one life for both CABG and PCI.

Although we agree that it would be useful to present confidence intervals around our numeric estimates, there are two reasons we have not. First, constructing statistically robust intervals around the estimates is extremely difficult because of multiple sources of variability in our analysis. Three of the prominent sources include: (1) variability in both the estimates of total cases and deaths averted resulting from the sampling design used in our dataset, the HCUP National Inpatient Sample, that allows national estimates based on a subset of hospitals and states, (2) variability in the relationship between hospital volume and patient mortality that is estimated via survey design-adjusted logistic regression, and (3) variability resulting from the lack of detail on the national implementation of a volume-based referral policy. Separate from the specific statistical concerns is that the size of our data set may afford a statistical precision that may overstate the true precision of our estimate given the host of factors which might alter the implementation of a national policy of CABG and PCI regionalization.
Response to Comments from Reviewer 2, Brahmajee Nallamothu

General:
The manuscript by Epstein et al. is an analysis of volume-based referral strategies for CABG and PCI in the United States. It uses NIS HCUP data from 1998-2001 to estimate the potential impact of the Leapfrog Group’s evidence-based hospital referral guidelines. The authors found that although in-hospital mortality was higher at low-volume facilities, the number of patients that would need to be referred to prevent a single death was 230 for CABG and 805 for PCI. They conclude that volume-based referral strategies would prevent fewer deaths than previously reported and makes it difficult to justify the resources required for their implementation. The manuscript is very well-written. The analysis appears appropriate and the tables complement the manuscript text. Their findings are important and their conclusions seem reasonable. I have only a few comments. No response required.

Major Compulsory Revisions:
None

Minor Essential Revisions:
1) Epstein et al. cite an article by Birkmeyer and Dimick to make their argument that earlier works may have overestimated the benefits of volume-based referral strategies. They note that the Birkmeyer and Dimick article suggested that for PCI a volume-based referral strategy would have needed to move 91,153 patients in 2000 to avert 547 deaths (i.e., 167 patients referred to prevent a single death). These numbers are dramatically different from Epstein et al.’s results. Can the authors expand on why they believe such a large difference exists between the two studies? Both used NIS and risk-adjusted models that include age, gender, acuity and co-morbidities and seemed to account for clustering effects. It seems unlikely that the difference is due to the additional years of data in the Epstein et al. article. Was it because Epstein et al. limited their data to large MSAs or that they included concomitant valve procedures?
For PCI, the difference in deaths averted does not appear to be driven by differences in the sample construction. Birkmeyer and Dimick (Surgery, 2004) count 678,296 PCI cases nationwide, 91,153 of which are in low-volume hospitals, and we count 625,199 PCI cases nationwide, 87,661 of which are in low-volume hospitals. The principal explanation for why the two estimates of PCI deaths averted differ is related to the methodology for calculating the expected mortality benefit from moving a PCI case from a low-volume hospital to a high-volume one. Birkmeyer and Dimick assume that all PCI cases in low-volume hospitals will benefit equally from a move to high-volume hospitals based on the average difference in risk-adjusted mortality. Applying their average reduction from 2.0% in low-volume centers to 1.4% to high-volume centers to their 91,153 low-volume cases yields their estimate of 547 deaths averted. In contrast, we model the volume-mortality association among patients treated in low-volume hospitals using a logarithmic relationship and allow for each patient’s expected mortality benefit to depend also on his comorbidity vector. Among PCI patients in low-volume centers, those
treated in centers with relatively higher volumes are assumed to experience a relatively smaller mortality benefit from transfer compared with those in relatively lower volumes. As there are disproportionately more patients in these higher-volume low-volume centers, our estimate of the net mortality effect is smaller than Birkmeyer and Dimick’s.

The first paragraph of the discussion section (p. 9) has been augmented to reflect this:

Differences between our estimates and previous ones are driven more by methodology than data. Whereas previous studies assumed that all patients moved from low- to high-volume centers would receive the same average mortality benefit, our methodology allowed the expected benefit for each patient at a low-volume center to depend on the volume of the center and the presence of patient comorbidities.

Further, the differences between our estimates of total cases and deaths averted and those of Birkmeyer and Dimick (Surgery, 2004) are actually quite small for CABG. We estimate 374,234 CABG cases nationally and 619 deaths averted; they estimate 394,165 CABG cases and 594 deaths averted.

2) The authors should expand on their discussion of the use of volume-based referral strategies in today’s healthcare environment. It should be noted that the Birkmeyer and Dimick article (see above) concluded that the use of volume-based criteria alone was inadequate for referral strategies in CABG and PCI. Their assessment was that risk-adjustment methods and other criteria based on processes and outcomes are likely to be superior. Do the authors agree with this conclusion or do they believe that all referral strategies are likely to be unsuccessful? Since most groups (including the Leapfrog Group) have largely moved away from the exclusive use of volume in their referral strategies, the authors’ comments on these issues would be more up-to-date and of great interest to the reader.

Based on the Birkmeyer and Dimick analysis, it appears that an approach blending hospital volume and risk-adjusted mortality to identify referral targets might be more efficient in terms of deaths averted per cases moved. However, we believe an appropriate comment on hospital referral strategies based on risk-adjusted mortality requires an entirely separate series of analyses than those incorporated in our manuscript. Given that risk-adjusted mortality for CABG or PCI is not readily available for all hospitals, whether to base referral strategies on volume remains a relevant question for policy-makers.

3) The authors included valve procedures in their risk-adjusted models for CABG. Were other concomitant open-heart surgeries such as thoracic aortic repairs identified or excluded in their patient populations?

As indicated in the Study Sample section, we included any hospital admission with a CABG in our analysis. We did not identify or exclude admissions on the basis of concomitant procedures, because these CABG procedures, even if they include other OHS procedures such as valve replacements, do contribute to each center’s CABG experience. We have, however, incorporated
a covariate in our model that distinguishes CABGs conducted in isolation and those with concomitant OHS procedures (ICD-9 CM procedure code 35) to adjust for differences in center case mix.

4) Is the IMA graft rate reported in Table 1 (Page 2) correct? This is alarmingly low and not consistent with national registry data that suggest a usage rate of 75% in 2000 (Ferguson TB et al. JAMA 2003). If correct, it implies that this variable is either inadequate captured or undercoded in NIS. What impact did the inclusion of this variable have on their results?

Thanks to Dr. Nallamothu for noticing this. After detecting an error, we corrected the algorithm used to identify whether CABG procedures included IMA grafts. This led to substantially increased rates of IMA graft use that were consistent with the expectations of reviewers 2 and 3. Table 1 shows that IMA grafts were used in about 77% of CABG procedures.

The risk-adjusted models were re-estimated, and the results have been updated accordingly. The risk-adjusted association between low CABG volume (<450 cases annually) and in-hospital mortality was materially unchanged (the point estimate was unchanged and the 95% CI moved by 0.01) as shown in Table 2. Correcting the IMA graft rate led to a minor change in the estimate of CABG deaths averted from the volume-based referral policy. The deaths averted estimate dropped by 6 deaths, from 625 to 619, leading to a marginal increase in the number of procedures needing to be moved to avert a single death, from 230 to 232 (Table 3). This changed the percent reduction in deaths from 4.58% to 4.54%.

Discretionary Revisions:
1) Did the authors consider exploring other thresholds for a volume-based referral strategy besides the Leapfrog Group’s recommendation? For example, the Leapfrog Group’s threshold of 450 annual cases for CABG has been criticized as overly strict. In addition, it appears from earlier studies that the greatest difference in in-hospital mortality rates exist between low- and high-volume hospitals at the extremes of volume. It might therefore be reasonable to refer patients from very-low volume hospitals only (i.e., less than 100, 100-250, 250-450 for CABG). An additional analysis could explore that hypothesis and even determine if an empirical threshold exists at which volume-based referral strategies may become worthwhile.

This analysis focused on the Leapfrog Group’s recommended volume thresholds because they were the most policy relevant at the time of the analysis. Based on evidence that patients in the lowest volume hospitals have the most to gain from transfer, lowering the volume threshold as proposed would yield a program that likely averted fewer deaths but did so in a more efficient manner. Although we agree with Dr. Nallamothu that such an analysis would be interesting and arguably of important policy relevance, a thorough investigation of this issue would necessarily require the consideration of a host of other issues that are outside the scope of this analysis. This is an interesting hypothesis that merits exploration in future work.
Response to Comments from Reviewer 3, Michael Mack

General:
This retrospective analysis of an administrative discharge database (NIS) by a well recognized group that concludes that establishment of procedure volume minimums for CABG and PCI in the U.S. would result in fewer deaths than previously estimated and that a policy requiring transfer of large numbers of patients to high volume institutions is questionable. I have a number of comments and questions for the authors that may improve the manuscript.
No response required.

Major Compulsory Revisions
1. Included in the study population was CABG with valve procedures. Most outcomes analyses of CABG do not include concomitant valve procedures, which comprise 10.6% of the patients in this study. Since addition of valve repair or replacement at least triples or quadruples the operative mortality, this introduces a possibly unfair bias into the study. The overall CABG mortality in this study of 3.6% is higher than most all comer databases (STS 2.9%, HCA 2.7%) and may be accounted for by inclusion of CABG plus valve patients. It would also be my assessment that CABG plus valve repair probably carries a significantly higher mortality in low volume hospitals than in high volume hospitals and perhaps the mortality benefit in high volume institutions would not be as great if CABG plus valve were not included.

We have three reasons for including CABGs with same-stay valve procedures. First, we do so for comparability with prior evaluations of volume-based hospital referral strategies, which do not differentiate CABGs with and without valve procedures (e.g., Birkmeyer and Dimick, Surgery, 2004; Birkmeyer, Finlayson and Birkmeyer, Surgery, 2001). Second, any real-world referral strategy that moved all isolated CABGs to high-volume hospitals would likely change referral patterns substantially for all non-isolated CABGs as well. We do not exclude CABG plus valve procedures because we are interested in evaluating the effects of a fully-implemented, nationwide referral program. Finally, consistent with our other, intentionally generous assumptions, the nature of the bias proposed above results in our estimate of CABG deaths averted from a national volume-based referral policy being an upper bound. Excluding CABG plus valve procedures could lead to the counter-charge that we were underestimating the benefits of a volume-based referral strategy. We have controlled for concomitant valve procedures in our regression model to account for the fact that these cases are higher risk on average. If CABG plus valve procedures lead to higher mortality when performed at low-volume versus high-volume hospitals, then arguably these procedures ought to be performed at high-volume hospitals.

We conducted a secondary analysis that addresses Dr. Mack’s concerns by estimating the effects of a volume-based policy that excluded CABG patients with concomitant valve procedures (ICD-9 CM procedure code 35) or same-stay PCI (a concern that Dr. Mack notes in comment #2 below). Crude mortality after limiting the CABG population to those without concomitant valve procedures or same stay PCI was lower (2.8%) than it was in the cohort that included these patients (3.6%). In both cases, lower volume hospitals had higher crude in-hospital mortality.
than high volume hospitals (“restricted CABG” cohort: 3.1% for low-volume hospitals and 2.6% for high-volume hospital; “full CABG” cohort: 3.9% for low-volume hospitals and 3.5% for high-volume hospitals). In multivariable analysis, we found that being treated at a low volume CABG hospital was associated with a modestly higher risk of mortality in the “restricted CABG” cohort (1.21, 95% CI 1.13-1.29) as compared with that estimated in our current analysis using the “full CABG” cohort (1.16, 95% CI 1.10-1.24).

We believe this modest difference in risk associated with CABG at a low volume hospitals results in only a minor modification in our principal findings concerning the impact of a CABG regionalization policy. First, the estimated number of cases needing to be diverted from low volume hospitals to high volume hospitals would decrease from 143,687 (in the “full CABG” cohort) to 125,446 (for the “restricted CABG” cohort). The estimated number of deaths averted would decline from 619 (the “full CABG” cohort estimate) to 480 (the “restricted CABG” cohort). Ironically, estimation of the benefit of CABG regionalization in the “restricted CABG” cohort would lower the efficiency of this strategy from its current estimate of 232 cases needing to be transferred to avoid a single death (the “full CABG cohort” estimate) to 420 cases. Because we have tried to construct a “best case” mortality reduction estimate for volume-based regionalization, we have elected to retain our estimation of CABG mortality benefits from the “full CABG” cohort.

2. Similarly, inclusion of same admission CABG and PCI in the CABG volume probably unfairly biases the low volume hospitals. Since half of same admission CABG/PCIs are usually for emergent CABG for failed PCI, the higher percent of same admission PCI in low volume hospitals (3.3% versus 2.8%) may adversely effect the assessment of CABG outcomes in low volume hospitals. As more patients in the low volume hospitals present with an acute myocardial infarction than in high volume tertiary care centers this unfairly biases the low volume institution outcomes. Acute emergent PCI followed by emergent CABG as a salvage situation in these acute MI patients again may prevent an unbiased comparison between and high volume CABG hospitals.

Please see our response to the prior comment.

3. The internal mammary artery graft percentages in Table 1 are clearly wrong. The overall internal mammary artery graft use of 16.8% is either an egregious error or I am interpreting the Table wrong. I assume that this number represents a percent and if so, according to the STS National Clinical Database as well as the HCA Casemix Database the percent of patients receiving an IMA should be approximately 80%. I assume this represents a coding error or an unclear labeling of the Table, which I am not understanding â€“ either way, this number needs to be clarified.

The error in the IMA graft percentages has been corrected and the analysis updated accordingly, as detailed in our response to the same point from Reviewer 2. We thank Dr. Mack for his vigilance.
4. The same comments hold true for PCI. Low volume hospitals are more likely to have patients undergoing PCI for acute myocardial infarction compared to high volume tertiary care centers. PCI at the time of acute MI is an independent variable associated with higher mortality and not necessarily hospital nor operator volume dependent. Patients undergoing emergent PCI for acute MI should be excluded. Unfortunately our administrative database does not include the clinical detail necessary to distinguish emergency and non-emergency PCI. Nevertheless, as elective PCIs likely constitute a higher portion of a high-volume center’s PCI caseload, including these cases in our analysis permits us to conclude that even under very generous assumptions the number of PCI cases requiring transfer to avert a single death is extremely high.

Minor Essential Revisions:
7. Reference 26 is incomplete.
This has been corrected.

Discretionary Revisions
5. A shortcoming of this study is the inability to assess operator specific volumes. As has been noted in the Discussion and multiple references, the best outcomes are obtained by high volume operators at high volume institutions. In analysis of New York state database by Hannan, 49% of the benefit of a high volume institution was solely due to the high volume operators. Any statements regarding institution volume is somewhat compromised by the inability to analyze by operator volume. Many low volume institutions have only 1 or 2 high volume operators while many high volume institutions have a number of low volume operators.
As we acknowledge in the limitations, the NIS does not identify individual operators. Thus we cannot determine what proportion of the variation in mortality we attribute to differences in institution-level volume may in truth reflect the differential distribution of operator volume. However, we believe our study’s findings remain relevant given that several groups, including Leapfrog, continue to advocate for the adoption of hospital volume thresholds divorced from any similar thresholds for operators. It was policies such as these that we sought to address in our study. Although operator volume likely plays a role in patient outcomes (Birkmeyer et al., N Engl J Med, 2003), for the purpose of this analysis it is of secondary importance.

6. The Discussion of the manuscript is appropriately quite circumspect and does appropriately call into question implementation of policies based upon procedural volume. The authors state however on page 11 under Limitations that there is no comprehensive national representative registry of cardiovascular procedure use. In point of fact, such a registry does exist â€” the STS National Clinical Database, which is a registry of 70% of all CABG procedures in the United States is a general source of data at least for CABG volumes and can be analyzed on the basis of individual operator volume. This database has recently been adopted by the NQF as the standard clinical outcomes source. We apologize for this omission. We have revised the sentence so that it now reads:
Previous studies, however, have demonstrated that administrative databases contain sufficient information to evaluate hospital differences in procedure quality,[25] and the NIS is a comprehensive, nationally representative, all-payer database that includes information on cardiovascular procedure use.

8. An assumption also made in this analysis is that there is no adverse mortality outcome associated with pre-procedural transfer to a high volume hospital and the time delay associated in the procedure necessitated by such a transfer. Do the authors have any information regarding potential mortality associated with transfer from a low volume to a high volume institution that may further diminish the potential of beneficial effect of transfer?

We do not have any specific information on the impact of transfer on mortality. This would play a role primarily in emergent cases, which we cannot reliably identify in our data. Nevertheless, by assuming no mortality effect associated with transfer, our estimates of deaths averted represent a conservative estimate of the number of deaths likely averted from treating patients at high volume hospitals.